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CLINICAL THERAPEUTICS

Clinical Benefit of Appropriate Empirical Fluoroquinolone Therapy for Adults with Community-Onset Bacteremia in Comparison with Third-Generation-Cephalosporin Therapy

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ABSTRACT Both fluoroquinolones (FQs) and third-generation cephalosporins (3rd-GCs) are commonly prescribed to treat bloodstream infections, but comparative efficacies between them were rarely studied. Demographics and clinical characteristics of 733 adults with polymicrobial or monomicrobial community-onset bacteremia empirically treated by an appropriate FQ ($n = 87$) or 3rd-GC ($n = 646$) were compared. A critical illness (respectively, 8.0% versus 19.0%; $P = 0.01$), an initial syndrome with severe sepsis (33.3% versus 50.3%; $P = 0.003$), or a fatal outcome at 28 days (4.6% versus 10.5%; $P = 0.08$) was less common in the FQ group. A total of 645 (88.0%) patients were febrile at initial presentation, and the FQ group with (FQ group versus 3rd-GC group, respectively, 7.6 days versus 12.0 days; $P = 0.04$) and without (3.8 days versus 5.4 days; $P = 0.001$) a critical illness had a shorter time to defervescence than the 3rd-GC group. By the propensity scores, 87 patients with appropriate FQ therapy were matched with 435 treated by 3rd-GC therapy at a ratio of 1:5, and there were no significant differences in terms of bacteremia severity, comorbidity severity, major comorbidities, causative microorganisms, and bacteremia sources between groups. Moreover, crude mortality rates at 28 days (FQ group versus 3rd-GC group, respectively, 4.6% versus 7.8%; $P = 0.29$) did not differ significantly. However, the time to defervescence was shorter in the FQ group (4.2 ± 3.6 versus 6.2 ± 7.6 days; $P < 0.001$). Conclusively in the adults with community-onset bacteremia, appropriate empirical FQ therapy was related to shorter time to defervescence than with 3rd-GC therapy, at least for those without a critical illness.

KEYWORDS fluoroquinolone, third-generation cephalosporin, empirical therapy, community onset, bacteremia, defervescence

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Bacteremia is associated with high morbidity and mortality that are associated with significant health care costs (1). Community-onset bacteremia is a common infectious disease, with an annual incidence of 0.82% in a population-based investigation (2). Generally, several Gram-positive and Gram-negative pathogens, such as staphylococci, streptococci, *Escherichia coli*, and *Klebsiella pneumoniae*, are major causative microorganisms of community onset bacteremia (2, 3).

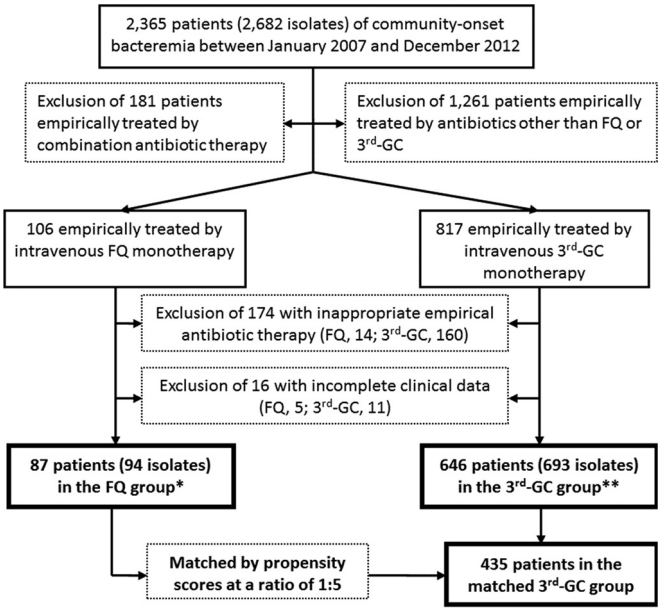

FIG 1 Patient selection flowchart. FQ, fluoroquinolone; 3rd-GC, third-generation cephalosporin. Patients in the FC group included 36 treated with levofloxacin, 35 treated with ciprofloxacin, and 16 treated with moxifloxacin (*). Patients in the 3rd-GC group included 303 patients treated with cefotaxime, 283 treated with ceftriaxone, and 60 treated with ceftazidime (**).

Fluoroquinolones (FQs) have a broad spectrum of antibacterial activity against Gram-negative and Gram-positive aerobes (4). Thus, clinical applications of FQs largely employed their potent activities for the treatment of several community-onset infections, such as urinary tract infections, pneumonia, intra-abdominal infections, skin and soft tissue infections, and acute bacterial exacerbation of chronic bronchitis (5). Third-generation cephalosporins (3rd-GCs) have been established as appropriate treatment of various community-onset or community-acquired infections caused by susceptible organisms (6, 7). However, with respect to empirical therapy, no clinical study has verified the beneficial effects of FQ therapy compared to that with 3rd-GC therapy in adults with community-onset bacteremia. Therefore, we aimed to compare the therapeutic efficacies of appropriate empirical FQ and 3rd-GC therapies in the management of community-onset bacteremia.

RESULTS

Demographics and clinical characteristics of the study cohort. Of a total of 2,365 adults with community-onset bacteremia, 733 adults with community-onset bacteremia empirically intravenously treated by appropriate FQs (87 patients, 11.9%) or 3rd-GCs (646, 88.1%) were included according to the inclusion and exclusion criteria (Fig. 1). The mean age of subjects was 67.6 years, and 375 (51.2%) were female. Common comorbidities included hypertension (346 patients, 47.2%), diabetes mellitus (266, 36.3%), malignancy (192, 26.2%), chronic hepatitis (164, 22.4%), neurological disorder (135, 18.4%), liver cirrhosis (131, 17.9%), chronic kidney disease (119, 16.2%), and coronary artery disease (66, 9.0%). Common sources of bacteremia were urinary tract infections (258 patients, 35.2%), intra-abdominal infections (130, 17.7%), biliary tract infections (96, 13.1%), pneumonia (72, 9.8%), liver abscess (57, 7.8%), primary bacteremia (52, 7.1%), and skin and soft tissue infections (40, 5.5%).

Bacteremic isolates and susceptibility. Because of 243 polymicrobial and 2,122 monomicrobial bacteremia episodes, a total of 2,682 causative microorganisms from 2,365 patients were collected. Common pathogens included *E. coli* (974, or 36.3% of the isolates), *Klebsiella* species (372, 13.9%), *Staphylococcus aureus* (319, 11.9%), *Streptococcus* species (289, 10.8%), *Pseudomonas* species (91, 3.4%), *Enterococcus* species (90, 3.4%), *Proteus*

TABLE 1 Susceptibility of the common microorganisms causing community-onset bacteremia in adults

Microorganism (no. of aerobes/ no. of isolates)[a]	Susceptibility rate (total isolates, eligible isolates [%])[b]		
	Levofloxacin	Cefotaxime	Ceftazidime
Gram-negative aerobes (1,849/655)			
Escherichia coli (974/359)	84.3, 89.5	89.5, 96.6	89.8, 96.6
Klebsiella species (372/166)	94.1, 100	89.5, 95.8	90.2, 95.8
Pseudomonas species (91/5)	100, 100		95.7, 100
Proteus species (70/20)	86.1, 87.5	86.1, 93.8	86.1, 93.8
Salmonella species (59/30)	93.1, 93.3	96.6, 100	96.6, 100
Aeromonas species (45/19)	95.5, 93.3	93.3, 93.3	93.3, 93.3
Enterobacter species (39/15)	93.5, 100	90.3, 100	90.3, 100
Gram-positive aerobes (710/118)			
Staphylococcus aureus (319/35)	81.6, 100	63.0, 100[c]	
Streptococcus species (289/79)	97.8, 98.5	95.6, 97.1	

[a]In addition to Gram-negative aerobes and Gram-positive aerobes, anaerobes accounting for 4.6% of 123 organisms and 1.8% of 14 isolates were not tested for susceptibility.
[b]Values were calculated on the basis of a total of 2,682 isolates and 787 eligible isolates (the full cohort).
[c]The percentages of methicillin sensitivity among *S. aureus* isolates.

species (70, 2.6%), *Salmonella* species (59, 2.2%), *Aeromonas* species (45, 1.7%), and *Enterobacter* species (39, 1.5%). Of 319 *S. aureus* isolates, 37.0% (118 isolates) were resistant to methicillin, and extended-spectrum β-lactamase (ESBL) production was found in 5.6% (79) of 1,416 *E. coli*, *Klebsiella* species, and *Proteus mirabilis* (EKP) isolates. In contrast, of 787 isolates from 733 eligible adults, common pathogens included *E. coli* (359, or 45.6% of the isolates), *Klebsiella* species (166, 21.1%), *Streptococcus* species (79, 10.0%), *Staphylococcus aureus* (35, 4.4%), *Salmonella* species (30, 3.8%), *Proteus* species (20, 2.5%), *Aeromonas* species (19, 2.4%), *Enterobacter* species (15, 1.9%), *Vibrio* species (10, 1.3%), and *Pseudomonas* species (5, 0.6%). All 35 *S. aureus* isolates were susceptible to methicillin, and ESBL production was found for 0.7% (4) of 544 EKP isolates.

For 2,682 isolates from 2,365 patients with community-onset bacteremia and 787 isolates from 733 eligible patients, the susceptibility rates of common pathogens to cefotaxime, ceftazidime, and levofloxacin are demonstrated in Table 1. Overall, levofloxacin was active against 87.8% of 1,849 Gram-negative aerobes and 86.5% of 710 Gram-positive aerobes causing community-onset bacteremia. Cefotaxime or ceftazidime was active against 86.1% to 96.6% or against 86.1% to 96.6%, respectively, of different species of Gram-negative aerobes.

Comparisons of baseline characteristics between FQ and 3rd-GC groups. The comparisons of clinical characteristics presented at bacteremia onset in the FQ and 3rd-GC groups are shown in Table 2. The numbers of female or elderly patients with major pathogens, major sources of bacteremia, comorbidities, and comorbidity severity (McCabe classification) were similar between the two groups. Only primary bacteremia was more frequently observed in the FQ group, and a critical illness (Pitt bacteremia score of $\geq$4; FQ group versus 3rd-CC group, respectively, 8.0% versus 19.0%; $P = 0.01$) or an initial syndrome with severe sepsis (33.3% versus 50.3%; $P = 0.003$) or septic shock (8.0% versus 20.3%; $P = 0.006$) was less frequent in the FQ group.

Clinical characteristics and outcomes of FQ and 3rd-GC groups with and without a critical illness. According to Pitt bacteremia scores at bacteremia onset, all 733 eligible patients were categorized as either critically ill (score of $\geq$4; 130 patients, or 17.7%) or not critically ill (score of $<$4; 603, 82.3%). Clinical characteristics and outcomes of the individuals in the FQ and 3rd-GC groups were compared (Table 2). Irrespective of the presence or absence of critical illness, gender, old age, polymicrobial episodes, causative pathogens, types and severity of comorbidity and 3-day, 14-day, and 28-day crude mortality rates were similar in the two groups. Among those without a critical illness, only primary bacteremia was more common in the FQ group (13.8 for the FQ group versus 6.9% for the 3rd-GC group; $P = 0.03$). Of note, among 645 patients

TABLE 2 Clinical characteristics, responses, and outcomes for 733 adults with community-onset bacteremia[a]

Parameter	Value for the total cohort			Value for patients with Pitt bacteremia score of ≥4			Value for patients with Pitt bacteremia score of <4		
	FQ ($n = 87$)	3rd-GC ($n = 646$)	*P* value	FQ ($n = 7$)	3rd-GC ($n = 123$)	*P* value	FQ ($n = 80$)	3rd-GC ($n = 523$)	*P* value
Female gender (no. of patients [%])	44 (50.6)	331 (51.2)	0.91	3 (42.9)	63 (51.2)	0.72	41 (51.2)	268 (51.2)	1.00
Age of ≥65 yr (no. of patients [%])	50 (57.5)	402 (62.2)	0.39	6 (85.7)	82 (66.7)	0.43	44 (55.0)	320 (61.2)	0.29
Clinical profile (no. of patients [%])									
Polymicrobial episodes	7 (8.0)	44 (6.8)	0.67	1 (14.3)	11 (8.9)	0.50	6 (7.5)	33 (6.3)	0.69
Initial syndrome									
Severe sepsis	29 (33.3)	325 (50.3)	0.003	7 (100)	119 (96.7)	1.00	22 (27.5)	206 (39.4)	0.04
Septic shock	7 (8.0)	131 (20.3)	0.006	3 (42.9)	82 (66.7)	0.23	4 (5.0)	49 (9.4)	0.20
Major causative microorganisms									
Escherichia coli	45 (51.7)	314 (48.6)	0.59	3 (42.9)	52 (42.3)	1.00	42 (52.5)	262 (50.1)	0.69
Klebsiella species	15 (17.2)	151 (23.4)	0.20	2 (28.6)	27 (22.0)	0.65	13 (16.2)	124 (23.7)	0.14
Streptococcus species	10 (11.5)	69 (10.7)	0.82	1 (14.3)	13 (10.6)	0.56	9 (11.2)	56 (10.7)	0.88
Staphylococcus aureus	3 (3.4)	32 (5.0)	0.79	0 (0)	8 (6.5)	1.00	3 (3.8)	24 (4.6)	1.00
Proteus species	0 (0)	20 (3.1)	0.15	0 (0)	8 (6.5)	1.00	0 (0)	12 (2.3)	0.38
Major source of bacteremia									
Urinary tract infection	33 (37.9)	255 (34.8)	0.57	2 (28.6)	42 (34.1)	1.00	31 (38.8)	183 (35.0)	0.51
Biliary tract infection	13 (14.9)	83 (12.8)	0.59	0 (0)	11 (8.9)	1.00	13 (16.2)	72 (13.8)	0.55
Intra-abdominal infection	12 (13.8)	118 (18.3)	0.31	0 (0)	22 (17.9)	0.60	12 (15.0)	96 (18.4)	0.47
Primary bacteremia	11 (12.6)	41 (6.3)	0.03	0 (0)	5 (4.1)	1.00	11 (13.8)	36 (6.9)	0.03
Pneumonia	9 (10.3)	63 (9.8)	0.86	3 (42.9)	27 (22.0)	0.20	6 (7.5)	36 (6.9)	0.84
Major comorbidities									
Hypertension	47 (54.0)	299 (46.3)	0.18	6 (85.7)	55 (44.7)	0.05	41 (51.2)	244 (46.7)	0.44
Diabetes mellitus	26 (29.9)	240 (37.2)	0.19	3 (42.9)	42 (34.1)	0.69	23 (28.8)	198 (37.9)	0.12
Malignancy	22 (25.3)	170 (26.3)	0.84	4 (57.1)	33 (26.8)	0.10	18 (22.5)	137 (26.2)	0.48
Chronic kidney disease	18 (20.7)	101 (15.6)	0.23	1 (14.3)	17 (13.8)	1.00	17 (21.2)	84 (16.1)	0.25
Neurological disease	16 (18.4)	119 (18.4)	1.00	2 (28.6)	39 (31.7)	1.00	14 (17.5)	80 (15.3)	0.61
Chronic hepatitis	15 (17.2)	149 (23.1)	0.22	0 (0)	23 (18.7)	0.35	15 (18.8)	126 (24.1)	0.29
Liver cirrhosis	11 (12.6)	120 (18.6)	0.18	0 (0)	19 (15.4)	0.59	11 (13.8)	101 (19.3)	0.23
Ultimately or rapidly fatal comorbidity[b]	16 (18.4)	155 (24.0)	0.25	2 (28.6)	30 (24.4)	1.00	14 (17.5)	125 (23.9)	0.21
Clinical outcome									
Time to defervescence (days [mean ± SD])	4.2 ± 3.6	6.6 ± 7.9	<0.001	7.6 ± 5.4	12.0 ± 11.9	0.04	3.8 ± 3.3	5.4 ± 6.2	0.001
Defervescence within 5 days after antimicrobial therapy (no. of affected patients/total no. of patients [%])[c]	67/81 (82.7)	327/564 (58.0)	<0.001	5/6 (83.3)	40/102 (39.2)	0.08	62/75 (82.7)	287/462 (62.1)	0.001
Crude mortality rate (no. of patients [%])									
3-day	2 (2.3)	28 (4.3)	0.56	1 (14.3)	26 (21.1)	1.00	1 (1.2)	2 (0.4)	0.35
14-day	2 (2.3)	49 (7.6)	0.07	1 (14.3)	34 (27.6)	0.67	1 (1.2)	15 (2.9)	0.71
28-day	4 (4.6)	68 (10.5)	0.08	2 (28.6)	40 (32.5)	1.00	2 (2.5)	28 (5.4)	0.27

[a]Patients were empirically treated by appropriate fluoroquinolones or third-generation cephalosporins and categorized by critical (Pitt bacteremia score of ≥4) and less critical (Pitt bacteremia score of <4) illness.

[b]McCabe classification.

[c]Values represent adjusted patient totals: 645 febrile patients, including 108 with a Pitt bacteremia score of ≥4 and 537 with a Pitt bacteremia score of <4 at admission.

with febrile illness at initial presentation, the time to defervescence was shorter in the FQ group in patients with (7.6 days versus 12.0 days; $P = 0.04$) and without (3.8 days versus 5.4 days; $P = 0.001$) a critical illness than for the corresponding individuals in the 3rd-GC group.

Predictors of 28-day mortality. The association of clinical variables, including age, gender, bacteremia severity, bacteremia sources, type and severity of comorbidities, and causative pathogens with 28-day crude mortality was examined by univariate analysis in 733 patients (Table 3). Several variables were positively associated with 28-day mortality: an underlying fatal comorbidity (McCabe classification; odds ratio [OR], 3.65; 95% confidence interval [CI], 2.22 to 6.02; $P < 0.001$), critical illness (Pitt bacteremia score of ≥4; OR, 9.12; 95% CI, 5.42 to 15.33; $P < 0.001$), bacteremic

TABLE 3 Risk factors of 28-day mortality in 733 adults with community-onset bacteremia

Variable at bacteremia onset	Patient outcome (no. of patients [%])		Univariate analysis		Multivariate analysis	
	Death ($n = 72$)	Survival ($n = 661$)	OR (95% CI)[a]	*P* value	Adjusted OR (95% CI)	*P* value
Pitt bacteremia score of ≥4 at onset	42 (58.3)	88 (13.3)	9.12 (5.42–15.33)	<0.001	9.24 (5.16–16.53)	<0.001
Bacteremia source						
Pneumonia	21 (29.2)	51 (7.7)	4.93 (2.75–8.82)	<0.001	2.45 (1.58–4.82)	0.007
Urinary tract infection	13 (18.1)	245 (37.1)	0.37 (0.20–0.70)	0.001	0.32 (0.21–0.56)	0.001
Biliary tract infection	4 (5.6)	92 (13.9)	0.36 (0.13–0.98)	0.046	NS[b]	NS
Liver abscess	1 (1.4)	56 (8.5)	0.15 (0.02–0.90)	0.03	NS	NS
Ultimately or rapidly fatal comorbidity[c]	35 (48.6)	136 (20.6)	3.65 (2.22–6.02)	<0.001	2.76 (1.48–5.15)	0.001
Escherichia coli bacteremia	27 (37.5)	332 (50.2)	0.60 (0.36–0.98)	0.04	NS	NS
Major comorbidities						
Malignancy	34 (47.2)	158 (23.9)	2.85 (1.74–4.68)	<0.001	2.82 (1.37–5.78)	0.005
Liver cirrhosis	20 (27.8)	111 (16.8)	1.91 (1.10–3.31)	0.02	NS	NS

[a]OR, odds ratio; CI, confidence interval.
[b]NS, not significant.
[c]McCabe classification.

pneumonia (OR, 4.93; 95% CI, 2.75 to 8.82; $P < 0.001$), and comorbidities with liver cirrhosis (OR, 1.91; 95% CI, 1.10 to 3.31; $P = 0.02$) or malignancy (OR, 2.85; 95% CI, 1.74 to 4.68; $P < 0.001$). In addition, bacteremia due to biliary tract infections (OR, 0.36; 95% CI, 0.13 to 0.98; $P = 0.046$), liver abscess (OR, 0.15; 95% CI, 0.02 to 0.90; $P = 0.03$), or urosepsis (OR, 0.37; 95% CI, 0.20 to 0.70; $P = 0.001$) and *E. coli* bacteremia (OR, 0.60; 95% CI, 0.36 to 0.98; $P = 0.04$) were associated with a better outcome. Consequently, five variables, i.e., fatal comorbidity (McCabe classification; adjusted OR [aOR], 2.76; 95% CI, 1.48 to 5.15; $P = 0.001$), critical illness (Pitt bacteremia score of ≥4; aOR, 9.24; 95% CI, 5.16 to 16.53; $P < 0.001$), bacteremic pneumonia (aOR, 2.45; 95% CI, 1.58 to 4.82; $P = 0.007$), urosepsis (aOR, 0.32; 95% CI, 0.21 to 0.56; $P = 0.001$), and underlying malignancy (aOR, 2.82; 95% CI, 1.37 to 5.78; $P = 0.005$) were independently associated with 28-day crude mortality in the multivariate regression model (Table 3).

Characteristics, clinical response, and outcomes of propensity-score-matched cohort. Of the 646 patients with empirical 3rd-GC therapy, 435 were matched with 87 in the FQ group, with the closest propensity scores based on five independent predictors of crude mortality, as indicated in Table 3. After matching, no significant differences were noted between groups in terms of age, gender, bacteremia severity, type and severity of comorbidity, initial syndrome, etiological microorganisms, and bacteremia sources (Table 4). Furthermore, for the types of definitive antimicrobial agents, 3-day (FQ group versus 3rd-GC group, respectively, 2.3% versus 2.8%; $P = 1.00$), 14-day (2.3% versus 5.3%, $P = 0.41$), and 28-day (4.6% versus 7.8%, $P = 0.29$) crude mortality rates were similar. However, shorter periods of empirical intravenous (mean; 4.0 versus 5.3 days; $P < 0.001$) and total intravenous (mean; 8.6 versus 11.1 days; $P = 0.007$) antibiotic therapies were observed in the FQ group. Moreover, the time to defervescence (4.2 versus 6.2 days; $P < 0.001$) and length of hospital stays (10.6 versus 13.6 days, $P = 0.007$) were significantly shorter in the FQ group. In a survival analysis using Kaplan-Meier curves for febrile patients, a significant difference ($P = 0.001$) in the time to defervescence was found between the FQ and 3rd-GC groups (Fig. 2).

In the analysis of matched febrile adults with empirical FQ and 3rd-GC therapies (Fig. 3), no differences in the time to defervescence were observed within the FQ group ($F = 0.99$, df = [2, 78]; $P = 0.36$). Although the differences in the time to defervescence within the 3rd-GC group were significant ($F = 3.94$, df = [2, 378]; $P = 0.02$), the time to defervescence was longer for all 3rd-GCs, i.e., cefotaxime (5.2 days; $P = 0.04$), ceftriaxone (7.5 days; $P < 0.001$), and ceftazidime (5.6 days; $P = 0.03$), than for the FQ group (4.2 days).

Clinical predictors of defervescence within 5 days after antimicrobial therapy. Since the mean period between the initiation of appropriate antimicrobial therapy and

TABLE 4 Clinical characteristics and outcomes of patients with community-onset bacteremia

Characteristic	Value for the group[a]		
	FQ ($n = 87$)	3rd-GC ($n = 435$)	*P* value
No. (%) of females	44 (50.6)	240 (55.2)	0.43
Age (yr [mean ± SD])	65.7 ± 16.9	68.1 ± 15.7	0.20
Pitt bacteremia score of ≥4 at onset (no. of patients [%])	7 (8.0)	35 (8.0)	1.00
Clinical profile (no. of patients [%])			
Polymicrobial episode	7 (8.0)	25 (5.7)	0.42
Presence of major causative microorganisms			
Escherichia coli	45 (51.7)	218 (50.1)	0.78
Klebsiella species	15 (17.2)	105 (24.1)	0.16
Streptococcus species	10 (11.5)	52 (12.0)	0.90
Staphylococcus aureus	3 (3.4)	14 (3.2)	1.00
Ultimately or rapidly fatal comorbidity[b]	16 (18.4)	90 (20.7)	0.63
Major comorbidities			
Hypertension	47 (54.0)	203 (46.7)	0.21
Diabetes mellitus	26 (29.9)	161 (37.0)	0.21
Malignancy	22 (25.3)	111 (25.5)	0.96
Chronic kidney disease	18 (20.7)	68 (15.6)	0.25
Neurological disease	16 (18.4)	79 (18.2)	0.96
Chronic hepatitis	15 (17.2)	91 (20.9)	0.44
Liver cirrhosis	11 (12.6)	71 (16.3)	0.39
Major source of bacteremia			
Urinary tract infection	33 (37.9)	169 (38.9)	0.87
Biliary tract infection	13 (14.9)	51 (11.7)	0.40
Intra-abdominal infection	12 (13.8)	67 (15.4)	0.70
Primary bacteremia	11 (12.6)	32 (7.4)	0.10
Pneumonia	9 (10.3)	42 (9.7)	0.84
Administration duration (days [mean ± SD])			
Empirical intravenous therapy	4.0 ± 2.0	5.3 ± 4.6	<0.001
Total intravenous antibiotic therapy	8.6 ± 7.4	11.1 ± 10.4	0.007
Length of hospitalization stay (days [mean ± SD])	10.6 ± 8.4	13.6 ± 12.5	0.007
Clinical outcome			
Time to defervescence (days [mean ± SD])[c]	4.2 ± 3.6	6.2 ± 7.6	<0.001
Defervescence within 5 days after antimicrobial therapy (no. of patients [%])[c]	67 (82.7)	224 (59.1)	<0.001
Crude mortality			
3-day	2 (2.3)	12 (2.8)	1.00
14-day	2 (2.3)	23 (5.3)	0.41
28-day	4 (4.6)	34 (7.8)	0.29

[a]Patients were empirically treated by intravenous appropriate fluoroquinolone (FQ) or third-generation cephalosporin (3rd-GC) and matched by propensity scores at a ratio of 1:5.
[b]McCabe classification.
[c]Pecentages reflect the fact that a total of 62 afebrile patients (6 FQ patients and 56 3rd-GC patients) were excluded at admission.

defervescence in 522 matched patients was approximately 5 days, the benefit of rapid defervescence, which was arbitrarily defined as having defervescence within 5 days of antimicrobial therapy, was examined among 645 febrile adults with community-onset bacteremia (Table 5). In the multivariate regression analysis, appropriate empirical FQ therapy (aOR, 3.26; 95% CI, 1.74 to 6.08; $P < 0.001$) and bacteremia related to biliary tract infection (aOR, 2.02; 95% CI, 1.17 to 3.50; $P = 0.01$) were independently associated with defervescence within 5 days (Table 5). However, concurrent liver abscess (aOR, 0.27; 95% CI, 0.15 to 0.50; $P < 0.001$) or pneumonia (aOR, 0.52; 95% CI, 0.28 to 0.84; $P = 0.03$) and a critical illness (aOR, 0.38; 95% CI, 0.25 to 0.59; $P < 0.001$) were negatively linked to defervescence within 5 days.

DISCUSSION

The choices of empirical antimicrobial agents in primary care clinics may be influenced by many host variables, including prior antibiotic exposure, underlying diseases,

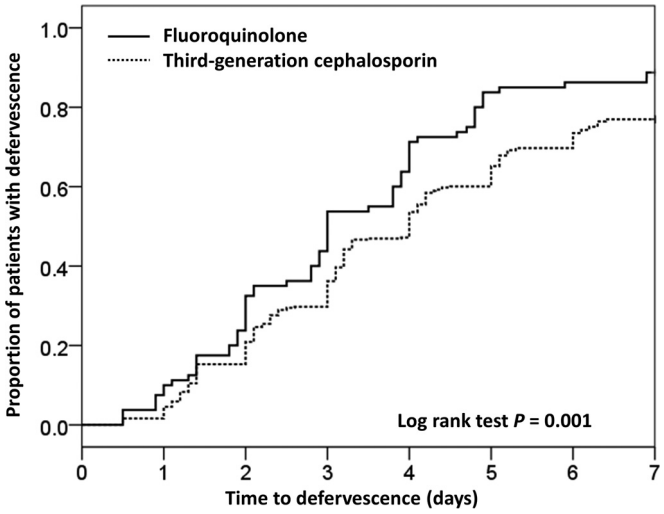

FIG 2 Kaplan-Meier curves of the time to defervescence in 453 survivors within 1 week after bacteremia onset who were empirically treated by intravenous fluoroquinolones or third-generation cephalosporins. Of the total group of 522 matched patients, 62 afebrile patients at bacteremia onset and 7 febrile patients who died within 7 days were excluded.

infection sources, bacteremia severity, or renal or hepatic dysfunction. Here, our patients with a critical illness at bacteremia onset were more likely to receive empirical 3rd-GC therapy, and thus a propensity score-matched analysis to control several covariates and to examine the association between the exposure of interest and the outcome (8) was conducted. Consequently, in our matched cohort there were no differences in terms of bacteremia severity, comorbidity type and severity, causative microorganisms, bacteremia source, and 14-day or 28-day crude or sepsis-related mortality, but the time to defervescence and the duration of intravenous antibiotic therapy and of hospital stays were shorter in patients with appropriate empirical FQ therapy. Prospective clinical trials are warranted to verify these therapeutic advantages in clinical practice.

Since baseline characteristics of the 3rd-GC and FQ groups were controlled by the propensity score matching, the matched cohort was not representative of the general population of community-onset bacteremia in which 20.2% of 2,365 adults had a Pitt bacteremia score of ≥4. In contrast, only 8.0% of 522 matched adults were critically ill.

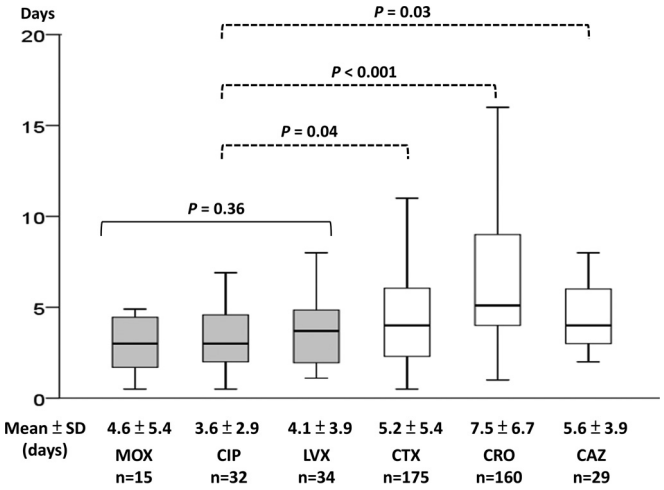

FIG 3 A box plot of the time to defervescence in 462 febrile matched patients empirically treated by a fluoroquinolone or third-generation cephalosporin. CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; CTX, cefotaxime; LVX, levofloxacin; MOX, moxifloxacin; SD, standard deviation.

TABLE 5 Clinical predictors linked to defervescence within 5 days after antimicrobial therapy among 645 febrile adults with community-onset bacteremia[a]

	Univariate analysis		Multivariate analysis	
Variable at bacteremia onset	OR (95% CI)[b]	*P* value	Adjusted OR (95% CI)	*P* value
Age of ≥65 years	0.95 (0.69–1.31)	0.74		
Female gender	1.04 (0.76–1.43)	0.79		
Pitt bacteremia score of ≥4	0.35 (0.23–0.54)	<0.001	0.38 (0.25–0.59)	<0.001
Ultimately or rapidly fatal comorbidity (McCabe classification)	0.97 (0.66–1.43)	0.89		
Polymicrobial episodes	1.16 (0.60–2.22)	0.66		
Appropriate empirical fluoroquinolone therapy	3.47 (1.90–6.32)	<0.001	3.26 (1.74–6.08)	<0.001
Major sources of bacteremia				
Biliary tract infection	2.37 (1.40–4.01)	0.001	2.02 (1.17 −3.50)	0.01
Urinary tract infection	1.31 (0.94–1.83)	0.11		
Intra-abdominal infections	1.20 (0.79–1.83)	0.40		
Skin and soft tissue infection	0.70 (0.35–1.41)	0.32		
Pneumonia	0.44 (0.25–0.77)	0.004	0.52 (0.28 −0.94)	0.03
Liver abscess	0.29 (0.16–0.52)	<0.001	0.27 (0.15–0.50)	<0.001
Major causative microorganisms				
Escherichia coli	1.67 (1.22–2.31)	0.002	NS[c]	NS
Streptococcus species	1.02 (0.60–1.73)	0.94		
Klebsiella species	0.58 (0.40–0.84)	0.004	NS	NS
Staphylococcus aureus	0.54 (0.25–1.15)	0.10		
Major comorbidities				
Chronic kidney disease	1.48 (0.93–2.36)	0.10		
Hypertension	1.24 (0.90–1.70)	0.19		
Liver cirrhosis	1.04 (0.68–1.58)	0.86		
Diabetes mellitus	1.00 (0.72–1.39)	0.99		
Neurologic disorder	0.97 (0.64–1.47)	0.89		
Malignancy	0.94 (0.65–1.35)	0.72		

[a]Patients were empirically treated with appropriate fluoroquinolones or third-generation cephalosporins.
[b]OR, odds ratio; CI, confidence interval.
[c]NS = not significant.

However, our further analyses support the beneficial effect of defervescence related to empirical FQ therapy. A shorter time to defervescence among adults receiving appropriate empirical FQ therapy than for those in the 3rd-GC group was evident not only for those with a critical illness but also for those without a critical illness.. Similarly, among febrile patients with community-onset bacteremia visiting the emergency department (ED) and empirically treated by an FQ or 3rd-GC, the multivariate regression analysis supports the advantage of rapid defervescence related to empirical FQ therapy.

Using multivariate regression, several independent risk factors of short-term mortality were recognized and assigned for scoring of the propensity match. Of importance, these predictors, including bacteremia severity at onset (9–11), comorbidity severity (9, 10), bacteremic pneumonia (10), and underlying malignancy (11, 12), have been evidenced in previous reports dealing with community-onset bacteremia. Additionally, another independent predictor linked to a better prognosis, urosepsis, was documented among patients with bacteremia onset in the ED (11).

Because FQs have a broad spectrum of antibacterial activity (4), their clinical applications are largely employed for major types of community-onset infection (5). Thus, numerous studies discussing their efficacy in comparisons with various beta-lactams were reported in the literature. Several previous studies indicated similar therapeutic efficacies of FQs and beta-lactams in patients with intra-abdominal infections (respectively, moxifloxacin and ceftriaxone plus metronidazole) (13), urinary tract infections (levofloxacin and doripenem) (14), acute bacterial exacerbation of chronic bronchitis (ciprofloxacin and cefuroxime) (15), and severe sepsis (ciprofloxacin and ceftazidime) (16). However, our study was the first to disclose the therapeutic benefit of FQ therapy in comparison with 3rd-GC therapy for bloodstream infections and also

the first report using propensity score matching. Such a finding was consistent with previous studies of community-acquired pneumonia (17, 18), in which a shorter period of time to defervescence or better clinical efficacy was observed in patients treated by FQs. It is likely that urinary tract infections, intra-abdominal infections, and pneumonia accounted overall for 67% of our study cases, and thus a similar outcome efficacy of empirical FQ and 3rd-GC therapies and an advantageous effect of FQ treatment on defervescence were recognized.

Even though FQ resistance was emerging in the community (4, 5), FQs remained active *in vitro* against >80% of *Enterobacteriaceae*, staphylococci, and streptococci in Taiwan and the Asia-Pacific region (19, 20), and the *Enterobacteriaceae* were major pathogens of community-onset bacteremia. In our study, levofloxacin was active *in vitro* against at least 80% of major causative microorganisms causing community-onset bacteremia and against 89 to 100% of the 787 isolates included in the empirical FQ and 3rd-GC groups. Accordingly, it is reasonable to choose FQ as the initial antimicrobial therapy for community-onset bacteremia to take advantage of rapid defervescence and shorter hospital stays.

Several limitations are inherent in the study design. First, three FQs and 3rd-GCs were grouped together though they varied in chemical structures, pharmacokinetic and pharmacodynamic characters, and antimicrobial spectra. However, our study found similar times to defervescence among the matched patients treated by levofloxacin, ciprofloxacin, or moxifloxacin. Therefore, the discrepancy in therapeutic efficacies among FQs for community-acquired bacteremia might be ignored. In contrast, the differences in the times to defervescence among 3rd-GCs were significant. However, the time to defervescence in the matched patients treated by cefotaxime, ceftriaxone, or ceftazidime was longer than that of the FQ group. Second, as a result of focusing on critically ill patients, the sample size in the FQ group is small ($n = 7$), thereby limiting the statistical power of comparisons between the FQ and 3rd-GC groups. However, the beneficial influence of appropriate empirical FQ therapy on defervescence remained significant despite the small sample size. Third, to assess the prognostic factors, patients for whom clinical information was incomplete were contacted by telephone for information retrieval. Only 1.7% (16) of 923 patients were excluded from our study for this reason. Therefore, the bias was considered to exert little influence on the results. Fourth, the negative impact of FQ prescription on promoting antimicrobial resistance or *Clostridium difficile* infection and the cost saving of rapid defervescence and early discharge were not evaluated. Fifth, even though levofloxacin as a representative FQ could be a reasonable alternative to empirical therapy in the treatment of community-onset bacteremia in the study hospital, our finding may not be generalized to other regions where FQ resistance is substantial. Finally, we investigated only short-term benefits of FQ therapy within 4 weeks after onset, and the long-term impact of FQ therapy remains obscure.

In conclusion, in the adults with community-onset bacteremia, appropriate empirical FQ therapy was related to a shorter time to defervescence than 3rd-GC therapy, at least for those without a critical illness.

MATERIALS AND METHODS

Study design and sites. This retrospective cohort study was conducted from January 2008 to December 2013 at the emergency department (ED) of a medical center in southern Taiwan. The study hospital is a 1,200-bed, university-affiliated medical center with an annual ED census of approximate 70,000 patients. The study was approved by the institutional review board of the hospital (A-ER-101-213), and informed consent was waived. The study results are reported according to a format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).

Patient population. During the study period, blood cultures sampled at the ED were screened for bacterial growth using a computer database. Medical information was retrieved for hospitalized cases of positive blood cultures. Adults with polymicrobial or monomicrobial community-onset bacteremia with empirical appropriate FQ or 3rd-GC therapy were included. Among the patients with multiple bacteremic episodes, only the first episode was included for each patient. Patients were excluded if they were empirically treated by combination therapy or inappropriate agents or if their clinical information was incomplete.

Data collection. By retrospective review of medical records of all eligible patients, the following information was collected in a predetermined case form: demographic and clinical data, including age, initial syndrome, vital signs at the ED, comorbidities, laboratory data, duration and type of antimicrobial agents, bacteremia source, length of hospital stay, bacteremia severity (Pitt bacteremia score) at onset, comorbidity severity (McCabe classification), date of defervescence, and patient outcome. The medical records were reviewed by two authors, and any discrepancy was discussed. The primary endpoint was the time to defervescence, and secondary endpoints included the duration of hospital stay, 3-day and 28-day crude mortality rates, and 28-day sepsis-related mortality rate.

Definitions. The term community-onset bacteremia indicates that the place of bacteremia onset was the community, which includes long-term health care facilities, as previously described (9). Because the susceptibility data were available approximately at 3 days after bacteremia onset, which was referred to as the timing of blood culture sampling, empirical antibiotic therapy was defined as the drug prescribed within 3 days after bacteremia onset, whereas definitive therapy referred to the antibiotic prescribed when the susceptibility result was available (9). Polymicrobial bacteremia was defined as the isolation of more than one microbial species from an episode. Defervescence was defined as an afebrile state in which tympanic body temperature remained at less than 37.0°C for at least 24 h, and the time to defervescence was defined as the period between defervescence and bacteremia onset. As previously described (21), antibiotic therapy was considered to be appropriate if the route and dosage of an antimicrobial agent were administered as recommended in the Sanford Guide (22) and if bacteremic pathogens were susceptible *in vitro* to the prescribed agent based on the contemporary breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) (23). Inappropriate empirical antibiotic therapy was defined as an instance in which the first dose of appropriate antimicrobial agent was not administered within the first 24 h after blood cultures were drawn (21). The bacteremia severity was graded according to the Pitt bacteremia score by a previously validated scoring system (24). Comorbidities were defined as before (25), and malignancies included hematological malignancies and solid tumors. The prognosis of underlying diseases was assessed by a previously delineated classification system (26). Bacteremia sources were determined clinically on the basis of the presence of an active infection site coincident with bacteremia or the isolation of a microorganism from other clinical specimens before or on the same date as that of bacteremia onset. If the bacteremia source could not be assigned to a specific site, it was classified as primary bacteremia.

Severe sepsis was defined as the coexistence of sepsis and at least one of the following signs or symptoms of acute organ dysfunction or hypoperfusion: metabolic acidosis, arterial hypoxemia (PaO_2 of $<$75 mm Hg or PaO_2/FiO_2 of $<$250), oliguria ($<$0.03 liters/h for 3 h or 0.7 liters/24 h), coagulopathy (increase in prothrombin time or a drop of platelet count by 50% or to $<100 \times 10^7$ platelets/liter), or encephalopathy (Glasgow coma score of $<$14) (27). Septic shock was defined as the presence of systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-min period or a blood lactate concentration of 4 mmol/liter or higher (27). Crude mortality was defined as death from all causes.

Microbiological methods. Blood cultures were incubated in a Bactec 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) for 5 days at 35°C. The species identification and *in vitro* antimicrobial susceptibility tests were assessed and analyzed by a semiautomated system. Species identification was determined by means of a Vitek 2 system (bioMérieux, Durham, NC). Bacteremic aerobic isolates in the study period were prospectively collected, and antimicrobial susceptibility was determined by the disk diffusion method, based on performance standards of CLSI in 2016 (23). The tested drugs included cefotaxime, ceftazidime, and levofloxacin. If a patient was empirically treated by other agents, such as ciprofloxacin, moxifloxacin, and ceftriaxone, the susceptibility of the specific drug was measured. For *E. coli*, *Klebsiella* species, and *Proteus mirabilis* (EKP), extended-spectrum beta-lactamase (ESBL) production was detected by a phenotypic confirmatory test with the cephalosporin-clavulanate combination disks recommended by CLSI in 2009 (28).

Statistical analyses. Statistical analyses were performed using the Statistical Package for the Social Science for Windows (version 20.0; Chicago, IL, USA). Demographic and clinical data, disease severity of comorbidities and bacteremia, and patient outcomes were compared by a Fisher exact or Pearson chi-square test for categorical variables and an independent *t* or Mann-Whitney test for continuous variables. One-way analysis of variance (ANOVA) was used to compare differences of the time to defervescence within the FQ or 3rd-GC group. To assess the independent predictors with adjusted odds ratios, the variables of 28-day mortality in the univariate analysis with a *P* value of less than 0.05 were included in a stepwise and backward multivariable logistic regression model. Kaplan-Meier curves and a log rank test were used to compare the effect of empirical antibiotics on the time to defervescence. A two-sided *P* value of less than 0.05 was regarded to be significant.

A propensity score-matched analysis was performed to control for confounding variables in the choice of empirical antimicrobial agents. The propensity score was calculated by the independent predictors of 28-day crude mortality assessed in a multivariable logistic regression model. Patients receiving appropriate empirical FQ therapy were matched by individual propensity scores at a ratio of 1:5 with those receiving appropriate empirical 3rd-GC therapy. The matching by the closest total scores was done manually based on a tolerance interval approach. As previously described (8), the matching tolerance was a propensity score difference of 0.2, implying that a patient with empirical FQ therapy was matched to one with empirical 3rd-GC therapy when the estimated probability of the latter receiving empirical FQ therapy was within 20% of the estimated probability of the counterpart of empirical 3rd-GC therapy.

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We declare that we have no conflicts of interest.

REFERENCES

1. Bates DW, Pruess KE, Lee TH. 1995. How bad are bacteremia and sepsis? Outcomes in a cohort with suspected bacteremia. Arch Intern Med 155:593–598.
2. Laupland KB, Gregson DB, Flemons WW, Hawkins D, Ross T, Church DL. 2007. Burden of community-onset bloodstream infection: a population-based assessment. Epidemiol Infect 135:1037–1042. https://doi.org/10.1017/S0950268806007631.
3. Chiu CW, Li MC, Ko WC, Li CW, Chen PL, Chang CM, Lee NY, Lee CC. 2015. Clinical impact of Gram-negative nonfermenters on adults with community-onset bacteremia in the emergency department. J Microbiol Immunol Infect 48:92–100. https://doi.org/10.1016/j.jmii.2013.08.004.
4. Hooper DC, Wolfson JS. 1991. Fluoroquinolone antimicrobial agents. N Engl J Med 324:384–394. https://doi.org/10.1056/NEJM199102073240606.
5. Hooper DC. 2000. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis 30:243–254. https://doi.org/10.1086/313677.
6. Brogden RN, Ward A. 1988. Ceftriaxone. A reappraisal of its antibacterial activity and pharmacokinetic properties, and an update on its therapeutic use with particular reference to once-daily administration. Drugs 35:604–645.
7. Jones RN, Thornsberry C. 1982. Cefotaxime: a review of in vitro antimicrobial properties and spectrum of activity. Rev Infect Dis 4(Suppl): S300–S315. https://doi.org/10.1093/clinids/4.Supplement_2.S300.
8. Austin PC. 2011. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 46:399–424. https://doi.org/10.1080/00273171.2011.568786.
9. Lee CC, Lee NY, Chen PL, Hong MY, Chan TY, Chi CH, Ko WC. 2015. Impact of antimicrobial strategies on clinical outcomes of adults with septic shock and community-onset *Enterobacteriaceae* bacteremia: de-escalation is beneficial. Diagn Microbiol Infect Dis 82:158–164. https://doi.org/10.1016/j.diagmicrobio.2015.03.004.
10. Hsieh CC, Lee CH, Li MC, Hong MY, Chi CH, Lee CC. 2016. Empirical third-generation cephalosporin therapy for adults with community-onset *Enterobacteriaceae* bacteraemia: impact of revised CLSI breakpoints. Int J Antimicrob Agents 47:297–303. https://doi.org/10.1016/j.ijantimicag.2016.01.010.
11. Lee CC, Lee CH, Chuang MC, Hong MY, Hsu HC, Ko WC. 2012. Impact of inappropriate empirical antibiotic therapy on outcome of bacteremic adults visiting the ED. Am J Emerg Med 30:1447–1456. https://doi.org/10.1016/j.ajem.2011.11.010.
12. Lin JN, Tsai YS, Lai CH, Chen YH, Tsai SS, Lin HL, Huang CK, Lin HH. 2009. Risk factors for mortality of bacteremic patients in the emergency department. Acad Emerg Med 16:749–755. https://doi.org/10.1111/j.1553-2712.2009.00468.x.
13. Weiss G, Reimnitz P, Hampel B, Muehlhofer E, Lippert H, AIDA Study Group. 2009. Moxifloxacin for the treatment of patients with complicated intra-abdominal infections (the AIDA Study). J Chemother 21: 170–180. https://doi.org/10.1179/joc.2009.21.2.170.
14. Naber KG, Llorens L, Kaniga K, Kotey P, Hedrich D, Redman R. 2009. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother 53:3782–3792. https://doi.org/10.1128/AAC.00837-08.
15. Chodosh S, McCarty J, Farkas S, Drehobl M, Tosiello R, Shan M, Aneiro L, Kowalsky S. 1998. Randomized, double-blind study of ciprofloxacin and cefuroxime axetil for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. Clin Infect Dis 27: 722–729. https://doi.org/10.1086/514930.
16. Peacock JE, Jr, Pegram PS, Weber SF, Leone PA. 1989. Prospective, randomized comparison of sequential intravenous followed by oral ciprofloxacin with intravenous ceftazidime in the treatment of serious infections. Am J Med 87:185S–190S. https://doi.org/10.1016/0002-9343(89)90055-7.
17. File TM, Jr, Segreti J, Dunbar L, Player R, Kohler R, Williams RR, Kojak C, Rubin A. 1997. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 41:1965–1972.
18. Welte T, Petermann W, Schurmann D, Bauer TT, Reimnitz P, MOXIRAPID Study Group. 2005. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis 41: 1697–1705. https://doi.org/10.1086/498149.
19. Hsueh PR. 2012. Study for Monitoring Antimicrobial Resistance Trends (SMART) in the Asia-Pacific region, 2002–2010. Int J Antimicrob Agents 40(Suppl):S1–S3. https://doi.org/10.1016/S0924-8579(12)00244-0.
20. de Lastours V, Fantin B. 2014. Resistance to fluoroquinolones in 2013: what are the consequences in internal medicine? Rev Med Interne 35:601–608. (In French.) https://doi.org/10.1016/j.revmed.2014.05.005.
21. Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, Gomez MJ, Del Arco A, Munoz A, Sanchez-Porto A, Torres-Tortosa M, Martin-Aspas A, Arroyo A, Garcia-Figueras C, Acosta F, Corzo JE, Leon-Ruiz L, Escobar-Lara T, Rodriguez-Bano J, SAEI/SAMPAC Bacteremia Group. 2012. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother 56:472–478. https://doi.org/10.1128/AAC.00462-11.
22. Gilbert ND, Moellering RC, Jr, Eliopoulos GM, Chambers HF, Saag MS. 2009. The Sanford guide to antimicrobial therapy. Antimicrobial Therapy, Inc., Sperryville, VA.
23. Clinical and Laboratory Standards Institute. 2016. Performance standards for antimicrobial susceptibility testing; twenty-sixth informational supplement. CLSI document M100-S26. Clinical and Laboratory Standards Institute, Wayne, PA.
24. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, Mulazimoglu L, Trenholme G, Klugman KP, Bonomo RA, Rice LB, Wagener MM, McCormack JG, Yu VL. 2004. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. Ann Intern Med 140:26–32. https://doi.org/10.7326/0003-4819-140-1-200401060-00008.
25. Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JT, van Weel C. 1993. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 46:469–473. https://doi.org/10.1016/0895-4356(93)90024-U.
26. McCabe WR. 1974. Gram-negative bacteremia. Adv Intern Med 19: 135–158.
27. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B. 1995. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 274:968–974.
28. Clinical and Laboratory Standards Institute. 2009. Performance standards for antimicrobial susceptibility testing; nineteenth informational supplement. CLSI document M100-S19. Clinical and Laboratory Standards Institute, Wayne, PA.